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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/549,250	05/18/2006	Carlos Garcia-Echeverria	ON/4-32910A	2465

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EXAMINER	
RAO, DEEPAK R	

ART UNIT	PAPER NUMBER
1624	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/549,250	GARCIA-ECHEVERRIA ET AL.	
	Examiner	Art Unit	
	Deepak Rao	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 July 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11 and 13-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11 and 13-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *20090325*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This office action is in response to the amendment filed on July 28, 2009.

Claims 1-11 and 13-24 are pending in this application.

Withdrawn Rejections/Objections:

Applicant is notified that any outstanding rejection/objection that is not expressly maintained in this office action has been withdrawn or rendered moot in view of applicant's amendments and/or remarks.

The following rejections are maintained:

1. Claims 14-22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating breast tumor comprising the step of administering a compound of formula (I), does not reasonably provide enablement for a method for treatment of neoplastic diseases and immune system disorders generally; or a method for the treatment or prevention of a disease which responds to inhibition of focal adhesion kinase and/or IGF-1R; or a method for the treatment or prevention of inflammatory and/or an immune disorder. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The reasons of the previous office action are incorporated here by reference.

Applicant's arguments have been fully considered but they were not deemed to be persuasive. Applicant argues that 'the instant claims are limited to those compounds disclosed and claimed in the present application and are not 'reach-through' claims because the

compounds of formula (I) are clearly disclosed and enabled in the specification'. This is not, however, deemed to be persuasive because as explained in the previous office action, the instant claims continue to be of the format drawn to mechanistic, receptor binding or enzymatic functionality and thereby reach through any or all diseases, disorders or conditions, for which they lack written description and enabling disclosure in the specification thereby requiring undue experimentation for one of skill in the art to practice the invention. Further, the claims continue to encompass numerous types of diseases and disorders and applicant did not state on record or provide any guidance that the assay provided is correlated to the clinical efficacy of the treatment of various disorders of the claims. The relevant portion from previous office action is provided below for convenience:

> The testing assays provided in the specification on pages 155-162 are related to FAK and ZAP-70 kinase inhibition in a standard coupled enzyme assay using 4T1 breast carcinoma cell line and biological results (in terms of IC50) of some of the tested compounds is provided in pages 164-170. Applicant did not state on record or provide any guidance that the assay provided is correlated to the clinical efficacy of the treatment of various disorders of the claims. As can be seen from specification page 20, the activity data holds significant role in determining the dosage regimen based on the minimal effective concentration of each of the compound to achieve the desired inhibition of the kinases.
>
> The instant claims are drawn to "a method for treatment of neoplastic diseases and immune system disorders generally; or a method for the treatment or prevention of a disease which responds to inhibition of focal adhesion kinase and/or IGF-1R; or a method for the treatment or prevention of inflammatory and/or an immune disorder". The use disclosed in the specification is as SYK and ZAP-70 kinase inhibitors, useful to treat a large list of diverse diseases, some of which are listed in pages 16-17 and 24-25. Test assays and procedures are provided in the specification in pages 155162 related to FAK and ZAP-70 kinase inhibition and it was concluded that the compounds of the invention exhibit inhibitory activity, however, there is nothing in the disclosure regarding how this *in vitro* data correlates to the treatment of the diverse disorders of the instant claims. The diseases and disorders encompassed by the instant claims include various types of tumors, CNS diseases, infectious diseases, autoimmune diseases, etc., some of which have been proven to be extremely difficult to treat. Further, there is no reasonable basis for assuming that the myriad of compounds embraced

by the claims will all share the same physiological properties since they are so structurally dissimilar as to be chemically non-equivalent and there is no basis in the prior art for assuming the same. Note *In re Surrey*, 151 USPQ 724 regarding sufficiency of disclosure for a Markush group.

Further, there is no disclosure regarding how all these assorted types diseases are treated. See MPEP § 2164.03 for enablement requirements in cases directed to structure-specific arts such as the pharmaceutical art. Receptor activity is generally unpredictable and highly structure specific area, as evidenced by the wide range of results obtained for the tested compounds. It is inconceivable as to how the claimed compounds can treat the large list of diseases embraced by the claims having diverse mechanisms.

For example, the instant claims are drawn to 'treating or **preventing** various types of tumors' which includes treatment of all types of cancers of blood, lymphocytes, etc. A 'cancer' is anything that causes abnormal tissue growth. That can be growth by cellular proliferation more rapidly than normal, or continued growth after the stimulus that initiated the new growth has ceased, or lack (partial or complete) of structural organization and/or coordination with surrounding tissue. It can be benign or malignant. Thus, such term covers not only all cancers, but also covers precancerous conditions such as lumps, lesions, polyps, etc. No compound has ever been found to treat cancers of all types generally. Since this assertion is contrary to what is known in medicine, proof must be provided that this revolutionary assertion has merits. The existence of such a "silver bullet" is contrary to our present understanding of oncology. Cecil Textbook of Medicine states that "each specific type has unique biologic and clinical features that must be appreciated for proper diagnosis, treatment and study" (see the enclosed article, page 1004). Different types of cancers affect different organs and have different methods of growth and harm to the body. Also see *In re Buting*, 163 USPQ 689 (CCPA 1969), wherein 'evidence involving a single compound and two types of cancer, was held insufficient to establish the utility of the claims directed to disparate types of cancers'. Thus, it is beyond the skill of oncologists today to get an agent to be effective against cancers generally. In reference to cancer treatment using protein tyrosine kinase inhibitors, Traxler (Exp. Opin. Ther. Patents, 1997) stated that "pharmacological properties such as stability in biological media, bioavailability, metabolism or formulability are significant hurdles" see page 585, col. 2, lines 33-36.

Enablement for the scope of "treatment or prevention of inflammatory disorders" generally is not present. For a compound or genus to be effective against inflammation generally is contrary to medical science. Inflammation is a process, which can take place individually any part of the body. There is a vast range of forms that it can take, causes for the problem, and biochemical pathways that mediate the inflammatory reaction. There is no common mechanism by which all, or even most, inflammations arise. Mediators include bradykinin, serotonin, C3a, C5a, histamine, assorted leukotrienes and cytokines, and many, many others. Accordingly, treatments for inflammation are normally tailored to

the particular type of inflammation present, as there is no, and there can be no "magic bullet" against inflammation generally. Inflammation is the reaction of vascularized tissue to local injury; it is the name given to the stereotyped ways tissues respond to noxious stimuli. These occur in two fundamentally different types. Acute inflammation is the response to recent or continuing injury. The principal features are dilatation and leaking of vessels, and recruitment of circulating neurophils. Chronic inflammation or "late-phase inflammation" is a response to prolonged problems, orchestrated by T-helper lymphocytes. It may feature recruitment and activation of T- and B-lymphocytes, macrophages, eosinophils, and/or fibroblasts. The hallmark of chronic inflammation is infiltration of tissue with mononuclear inflammatory cells. Granulomas are seen in certain chronic inflammation situations. They are clusters of macrophages, which have stuck tightly together, typically to wall something off. Granulomas can form with foreign bodies such as aspirated food, toxocara, silicone injections, and splinters. Otitis media is an inflammation of the lining of the middle ear and is commonly caused by Streptococcus pneumoniae and Haemophilus influenzae. Cystitis is an inflammation of the bladder, usually caused by bacteria. Blepharitis is a chronic inflammation of the eyelids that is caused by a staphylococcus. Dacryocystitis is inflammation of the tear sac, and usually occurs after a long-term obstruction of the nasolacrimal duct and is caused by staphylococci or streptococci. Preseptal cellulitis is inflammation of the tissues around the eye, and Orbital cellulitis is an inflammatory process involving the layer of tissue that separates the eye itself from the eyelid. These life-threatening infections usually arise from staphylococcus. Hence, these types of inflammations are treated with antibiotics. Certain types of anti-inflammatory agents, such as non-steroidal anti-inflammatory medications (Ibuprofen and naproxen) along with muscle relaxants can be used in the non-bacterial cases. The above list is by no means complete, but demonstrates the extraordinary breadth of causes, mechanisms and treatment (or lack thereof) for inflammatory disorders. It establishes that it is not reasonable to any agent to be able to treat inflammatory disorders generally.

The diagnosis of each of the disease is generally suggested by medical history and reports of endoscopy, cytology, X-ray, biopsy, etc. depending on the symptoms, signs and complications, which is essential to establish the dosage regimen for appropriate treatment or prevention. The disclosure does not provide any guidance towards the dosage regimen required to facilitate the treatment and/or inhibition of the claimed disorders, nor indicate competent technical references in the appropriate methods.

Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use of the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Traxler, in a recent article (Exp. Opin. Ther. Patents, 1997) stated that

"The concept of the inhibition of growth factor receptor-mediated signal transduction via inhibition of its protein tyrosine kinase is a novel, **not yet proven** clinical approach to the regulation of cell proliferation.", see page 585, col. 1. Therefore, the state of the art provides the need of undue experimentation for the instantly claimed therapeutic benefits.

Further, the instant claims are drawn not only to 'a method of treating' but also to '**a method of preventing**', for which the specification does not provide sufficient enablement. 'To prevent' actually means *to anticipate* or *counter in advance, to keep from happening etc.* (as per Websters II Dictionary) and therefore it is not understood how one skilled in the art can reasonably establish the basis and the type of subject to which the instant compounds can be administered in order to have the recited effect of **prevention**. Based on the inhibitory activity, the instant compounds are disclosed to be useful in the "prevention" of, for example, degenerative disorders, for which applicants provide no competent evidence. It is inconceivable from the *in vitro* data of a small number of representative compounds can be correlated to the "treating or **preventing**" of the various claimed disorders, such that the claimed compounds can not only treat but also "prevent" a myriad of diseases associated with the stated activity. Further, there is no evidence on record which demonstrates that the *in-vitro* screening test relied upon is recognized in the art as being reasonably predictive of success in any of the contemplated areas of "preventing". Such a reasonable correlation is necessary to demonstrate such utilities. See *Ex parte Stevens*, 16 USPQ 2d 1379 (BPAI 1990); *Ex parte Busse et al.*, 1 USPQ 2d 1908 (BPAI 1986) (the evidence must be accepted as "showing" such utility, and not "warranting further study").

Part of the difficulty of developing drugs effective for **preventing** any of the medical conditions such as tumors, CNS disorders, etc. lies in the lack of understanding as to why people come down with these disorders and the numerous causes of these disorders.

(Only a few of the claimed diseases are discussed here to make the point of an insufficient disclosure, it does not definitely mean that the other diseases meet the enablement requirements).

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the use of the invention. In view of the breadth of the claim, the chemical nature of the invention, the unpredictability of ligand-receptor interactions in general, and the lack of working examples regarding the activity of the claimed compounds, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the invention commensurate in scope with the claims.

Applicant further argues that 'the term "preventing" has been deleted' from the claims. This is not, however, found to be the case because claims 15 and 19 continue to recite "a method for the treatment or **prevention** ..." and therefore, continue to encompass 'a method of preventing'. For all the above reasons the rejection is maintained.

2. Claims 1-11 and 13-24 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-2, 4 and 7-9 of copending Application No. 10/507,060. The reasons from the previous office action are incorporated here by reference.

3. Claims 1-11 and 13-24 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 23-42 of copending Application No. 10/568,367. The reasons from the previous office action are incorporated here by reference.

It is acknowledged that applicant will address the double patenting rejections upon indication of allowable subject matter.

***The following rejections are necessitated by the amendment and/or under new grounds*:**

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2, 4 and 5 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following reasons apply:

1. In claim 2, the definition of R^3 is repeated, see page 4, lines 3-4 and 5-6. Deletion of one occurrence is suggested.
2. Claim 4 recites the limitation "the pair of adjacent substituents R^0 and R^1, or R^1 and R^2 is $-O-CH_2-O$" in line 7. There is insufficient antecedent basis for this limitation in claim 1 on which claim 4 is dependent. Claim 1 does not contain the limitation that adjacent substituents R^0 and R^1, or R^1 and R^2 together form a cyclic group.
3. Claim 5 recites the limitation "the pair of adjacent substituents R^0 and R^1, or R^1 and R^2 is $-O-CH_2-O$" in line 7. There is insufficient antecedent basis for this limitation in claim 1 on which claim 5 is dependent. Claim 1 does not contain the limitation that adjacent substituents R^0 and R^1, or R^1 and R^2 together form a cyclic group.

Claim Rejections - 35 USC § 103

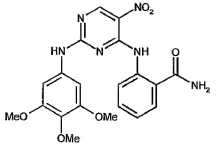
The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1-3, 10-11 and 13-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Davis-Ward et al., WO 2004/074244 (effective filing date: February 20, 2003).

The reference teaches pyrimidine-2,4-diamine compounds that are structurally analogous to instantly claimed compounds. See the compounds of formula (I) in page 3, wherein Y can be $-C(O)R^8$, $-S(O)_eN(R^9)_2$, etc. wherein R^8 is $-N(R^6)_2$, etc.; up to five R^5 substituents on the phenyl

ring which is at the 2-position of the pyrimidine ring attached via $-N(R^3)-$; and the corresponding species of the examples, see for example, the compound of Example 3, Example 5, etc. The compounds are taught to be useful as pharmaceutical agents, see pages 7-8. The instant claims differ from the reference by reciting specific species or a more limited subgenus than the reference. It would have been obvious to one having ordinary skill in the art at the time of the invention to select any of the species of the genus taught by the reference, including those instantly claimed, because the skilled chemist would have the reasonable expectation that any of the species of the genus would have similar properties and, thus, the same use as taught for the genus as a whole i.e., as therapeutic agents. One of ordinary skill in the art would have been motivated to select the claimed compounds from the genus in the reference since such compounds would have been suggested by the reference as a whole. It has been held that a prior art disclosed genus of useful compounds is sufficient to render prima facie obvious a species falling within a genus. *In re Susi*, 440 F.2d 442, 169 USPQ 423, 425 (CCPA 1971), followed by the Federal Circuit in *Merck & Co. v. Biocraft Laboratories*, 847 F.2d 804, 10 USPQ 2d 1843, 1846 (Fed. Cir. 1989).

Alternatively, the instantly claimed compounds require a non-hydrogen substituent at the *ortho* position (or 2-position) of the ring attached to the 2-amino group of the pyrimidine (i.e., in the claims R_{10} is required to be a non-hydrogen substituent as defined in the claims). The reference discloses specific pyrimidine compounds which contain substituents at the 3-, 4- and/or 5-positions, see the compounds of the examples 3, 5, etc. (a representative structure depicted below):



The reference, however, generically teaches that the substituent R^5 can be present at any of the ring carbons of the phenyl ring which is attached to the 2-position of the pyrimidine ring, attached via $-N(R^3)-$. The instant claims differ from the reference compounds by requiring a non-hydrogen substituent at a position different from the reference disclosed specific compounds, i.e., at the 2-position and therefore, the instantly claimed compounds are positional isomers of the reference compounds. It would have been obvious to one having ordinary skill in the art at the time of the invention to prepare the instantly claimed compounds because they are positional isomers of the reference compounds. One having ordinary skill in the art would have been motivated to prepare the instantly claimed compounds because such isomeric compounds are suggestive of one another and would be expected to share similar properties and therefore, the same use as taught for the reference compounds, i.e., as pharmaceutical agents. It has been held that a compound, which is structurally isomeric with a compound of prior art is prima facie obvious absent unexpected results. *In re Finley*, 81 USPQ 383 (CCPA 1949); *In re Norris*, 84 USPQ 458 (CCPA 1950); *In re Dillon*, 919 F.2d at 696, 16 USPQ2d at 1904 (Fed. Cir. 1990).

Receipt is acknowledged of the Information Disclosure Statement filed on March 25, 2009 and a copy is enclosed herewith.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deepak Rao whose telephone number is (571) 272-0672. The examiner can normally be reached on Monday-Friday from 8:00am to 5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson, can be reached at (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Deepak Rao/
Primary Examiner
Art Unit 1624

November 12, 2009